

BEST AVAILABLE COPY

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 July 2002 (18.07.2002)

PCT

(10) International Publication Number
WO 02/056006 A2

(51) International Patent Classification⁷: G01N 30/00

NJ 08819 (US). SCYPINSKI, Stephen; 50 Kinnan Way, Basking Ridge, NJ 07920 (US).

(21) International Application Number: PCT/US01/51024

(22) International Filing Date: 23 October 2001 (23.10.2001)

(74) Agents: JOHNSON, Philip, S. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933-7003 (US).

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/699,212 27 October 2000 (27.10.2000) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(71) Applicant: ORTHO-MCNEIL PHARMACEUTICAL, INC. [US/US]; U.S. Route 202, Raritan, NJ 08933-7003 (US).

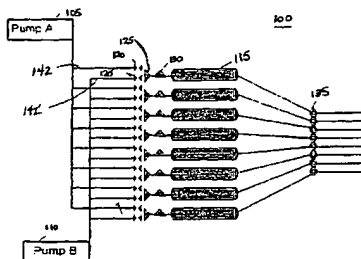
(72) Inventors: FERMIER, Adam, M.; 76 Highlands Boulevard, Easton, PA 18042 (US). HOCHMAN, Elias, H.; 5-3 Aspen Way, Doylestown, PA 18901 (US). GUZMAN, Norberto, A.; 17 Dellanbaugh Lane, East Brunswick,

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,

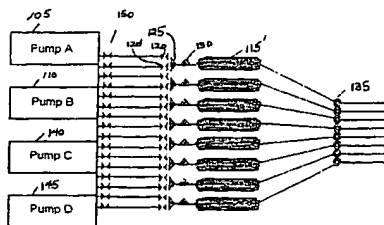
[Continued on next page]

(54) Title: HIGH THROUGHPUT HIGH PERFORMANCE CHROMATOGRAPHY SYSTEM

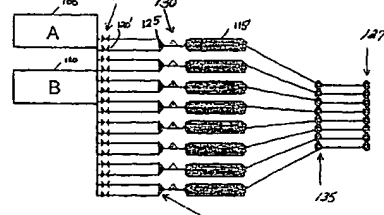
A



B



C



(57) Abstract: A high throughput high performance chromatography system operating at a high mixing pressure including a plurality of pressurized solvent reservoirs, e.g. pumps, each maintaining an associated solvent at a substantially constant pressure. A plurality of flow control valves are connected downstream or upstream of the reservoirs for controlling the flow rate of the solvent into the respective columns. The number of reservoirs equals the number of solvents. Accordingly, the system reduces the number of pumps required thereby saving money and space. Furthermore, the system increases sample throughput, accelerates method development and minimizes organic waste.

WO 02/056006 A2

BEST AVAILABLE COPY

WO 02/056006 A2



IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

- without international search report and to be republished upon receipt of that report

HIGH THROUGHPUT HIGH PERFORMANCE
CHROMATOGRAPHY SYSTEM

Field of the Invention

The present invention relates to a chromatography system, and in particular to a high throughput analytical chromatography system and method for operating the same to increase sample throughput and method development.

Description of Related Art

Separation science is a universal technique that benefits most scientists. Chromatographic separations provide a means to determine to what extent a reaction has yielded the desired products, to monitor impurities and dissolution profiles, and to study degradation pathways in drug products. Disadvantageously, chromatographic separations are relatively long and tedious processes with analysis times up to approximately 1 hour. Another problem associated with conventional chromatographic separations is the method development time. Screening multiple columns, materials and instruments to achieve optimum separation is labor intensive.

Heretofore, conventional analytical HPLC separation devices consist of a flow-metering pump to control volumetric flow rates of solvent gradients. Either low or high pressure mixing is used to produce the gradient. As the names imply, low pressure and high pressure mixing refer to the forming of the gradient either pre- or post-pump, respectively. To increase the capacity of the system it would be desirable to build an

instrument capable of running several columns in parallel. For example, for parallel processing of 8 columns, 8 conventional detectors would be required and, depending on how the gradient is formed, either 8 or 16 pumps would be required for low pressure and high pressure mixing, respectively. The increased number of pumps and detectors necessary for this set up is costly and would take up a significant amount of space.

It is therefore desirable to develop a parallel processing chromatographic separation system that would be more cost effective, take up less space and be convenient and easy to use by the operator. As a result, the sample throughput time would increase as the method development time decreases.

Summary of the Invention

For the purposes of the present invention the generic term high throughput high performance chromatography (HT-HPC) is defined to include high throughput high performance liquid, gas, capillary, microbore, preparative, electro, and supercritical fluid chromatography systems.

The present invention is directed to a HT-HPC system and method that solves the aforementioned problems and disadvantages associated with conventional serial systems and techniques.

The present invention is directed to a HT-HPC system that provides independent control of flow rates into an array of columns via flow control valves. Flow control valves are a convenient means to run multiple separations simultaneously, i.e., parallel processing, from common pressurized solvent reservoirs. The valves allow a manifold of columns to be analyzed in a high pressure mixing mode. The high pressure mixing mode

advantageously lowers gradient dwell time and subsequently allows faster equilibration and analyses times.

In accordance with the present invention, the HT-HPC system and technique is more efficient in that it requires less analysis and method development time due to its parallel configuration. Accordingly, the system and method in accordance with the invention can produce results in a shorter period of time because multiple samples can be run in the same period of time as a single sample using a conventional system.

Another advantage of the present invention HT-HPC system is the design of high pressure mixing for relatively low gradient dwell times.

The present invention is directed to a high throughput high performance chromatography system operating at a high mixing pressure including a plurality of pressurized solvent reservoirs, e.g., pumps, each maintaining an associated solvent at a substantially constant pressure. A plurality of flow control valves are connected downstream of the pressurized solvent reservoirs for controlling the flow rate of the solvent into each column. The number of pressurized solvent reservoirs equals the number of solvents. Accordingly, the system reduces the number of pressure solvent reservoirs required thereby saving money and space. Furthermore, the system increases sample throughput, accelerates method development and minimizes organic waste. In an alternative embodiment, instead of each valve being associated with a single column, a plurality of columns may be connected downstream of each valve to form an array, whereby the valves associated with a particular lane control the flow rate of the solvent into the columns associated with that lane. This adds another dimension to the separation capabilities of the instrument thereby

providing a very flexible instrument for method development and sample throughput. Additional dimensions may be added to the system, as desired.

Another embodiment in accordance with the present invention provides a s-shaped sample detection cell for measuring absorbance of the sample. The cell includes a section of tubing connected to the flow stream via two tees. Fiber optics deliver the light to the cell and directs the transmitted light from the cell to the detector. A single detector may be used for all parallel processed channels thereby reducing the cost and saving space.

Still another embodiment discloses a method for using the high throughput high performance chromatography system described above. One or more solvents are maintained at a substantially constant pressure using an associated pressurized solvent reservoir. The flow rate of the solvent into respective columns is controlled using a flow control valve connected downstream of each pressurized solvent reservoir. The gradient of each column may be independently adjusted.

Brief Description of the Drawings

The foregoing and other features of the present invention will be more readily apparent from the following detailed description and drawings of illustrative embodiments of the invention wherein like reference numbers refer to similar elements throughout the several views and in which:

Figure 1a is an exemplary 8 channel High Throughput High Performance Chromatography system in accordance with the present invention employing a gradient elution;

Figure 1b is an exemplary 8 x 8 High Throughput High Performance Chromatography array in accordance with the present invention;

Figure 1c is another exemplary 8 x 8 High Throughput High Performance Chromatography array in accordance with the present invention;

Figure 1d is an exemplary isocratic setup of an 8 channel High Throughput High Performance Chromatography array in accordance with the present invention;

Figure 2 is an exemplary flow metering system in Figures 1a- 1d;

Figure 3 is an isometric view of an exemplary sample detection flow cell in accordance with the present invention; and

Figure 4 is an exemplary detection system.

Detailed Description of the Invention

Figure 1a is an exemplary High Throughput High Performance Chromatography (HT-HPC) system 100 in accordance with the present invention using flow control valves rather than pumps for regulating the flow into each column. HT-HPC system 100 includes two pressurized solvent reservoirs 105, 110 delivering solvents A and B, respectively, at a substantially constant pressure to all 8 columns 115 through a manifold. Pressurized solvent reservoirs 105, 110 may be any conventional pump that is able to generate a head pressure, such as a syringe pump or a reciprocity pump. Alternatively, any device may be used that is able to provide a substantially constant pressure solvent source, such as an accumulator piston. Although the present invention is shown and described with respect to a chromatographic device having 8 columns and two solvents A, B, it is within the intended scope of the

present invention to use the device with any number of desired columns and/or solvents.

Since the configuration with respect to each column is the same, the arrangement associated with only the first column 115 will be described in detail. Pressurized solvent reservoirs 105, 110 are connected to column 115 by tubing 142, 142'. Unlike conventional HT-HPC devices in which the flow rate of the solvents into the columns is adjusted by pumps, the HT-HPC system in accordance with the present invention employs respective automated flow control valves 120, 120' to adjust the flow rate of solvents A, B, into the column 115. In a preferred embodiment, metering valves capable of controlling the flow below mL per minute, such as the QUANTIM Mass Flow Meter manufactured by Brooks Instrument, Inc., are used. Flow control valves 120, 120' comprise three basic components: a flow meter, a valve, and software/hardware to operate the valve. Conventional flow meters are turbine- temperature-, pressure- and mass-based flow meters. Integrated flow meters and valves are commercially available as flow control valves. These integrated flow control valves are relatively expensive. Alternatively, a less expensive high-pressure solenoid controlled using pulse width modulation, software and a flow meter capable of metering the desired flow range may be used. The use of valves instead of pumps, as in conventional HT-HPC systems, is beneficial in several respects. A substantially constant flow and pulseless rate may be realized by using a valve, which is otherwise impractical when using a pump. Because the valve produces a substantially constant flow source, precise or refined control over the flow rate is possible with less waste. Furthermore, the use of valves to control the flow rate allows the solvent streams to be split off and mixed

independently together to produce a user defined gradient for each lane from one or more common pressurized solvent reservoirs.

A high pressure mixing tee or gradient mixing chamber 125 connects the outputs from the automated flow metering valves 120, 120' and mixes together the two solvents A and B prior to entering the column 115. Disposed between the mixing tee 125 and column 115 is an injector 130 for introducing the sample into the column 115. Downstream of column 115 is a sample detection cell 135, for example, an ultraviolet detector, for detecting the absorbance data from each column.

The 8 channel parallel processing HT-HPC instrument shown in Figure 1a may be modified into an 8 x 8 array of HPC columns, as shown in Figure 1b. The 8 x 8 array has four pressurized solvent reservoirs 105, 110, 140, 145 for solvents A, B, C, D, respectively. A solvent selection valve 150 is disposed in each lane. This array provides greater versatility in that more columns may be analyzed in the same run. Although an 8 x 8 array is shown in Figure 1b, it is within the intended scope of the invention to configure an M x N array, where M and N ≥ 1 . Since only two flow control valves 120, 120' are provided for each lane, the gradient into each column may comprise at most two different solvents. Four flow control valves can be employed in each lane to produce a gradient that is a mixture of four or less solvents. Alternatively, as shown in Figure 1c, the flow meter 127 and flow control valve 120 may be located at two different locations in the flow stream to minimize the number of flow meters and pressure specifications.

Although a separation system in accordance with the present invention has been shown in Figures 1a, 1b, and 1c for gradient elution wherein the two or more

solvents form a gradient, it is within the intended scope of the invention to use the HT-HPC system for isocratic elution, that employs a single solvent of substantially constant composition. Figure 1d is an exemplary 8 channel High Throughput High Performance Chromatography system 600 employing an isocratic elution. Since a single solvent of substantially constant composition is employed, only a single pressurized solvent reservoir 105 and one flow metering valve 120 for each lane is required.

The flow rates of solvent into each column of Figures 1a, 1b, 1c, and 1d are controlled by flow control valves. As previously mentioned, flow control valves comprise of three basic components: a flow meter, a valve, and software/hardware to operate the valve. Conventional flow meters are turbine- temperature-, pressure- and mass-based flow meters. Figure 2 is an exemplary flow control valve including a pressure based flow meter, stepper driven valve and a computer. The configuration shown in Figure 2 is a single channel instrument. This configuration can be associated with column 115 in the column array in Figures 1a-1d. The same flow control valve arrangement is employed for each of the 8 columns in the array. Solvent from the pressurized solvent reservoirs 105, 110 flows through the tubing 142, 142' respectively, to the column 115. A first pair of pressure transducers 140, 145 and 140', 145' are disposed along the tubing 142, 142', respectively. Each pair of pressure transducers measures the respective pressure differential across a predetermined length of the tubing. The volumetric flow rate Q can be derived knowing the measured pressure drop using the Hagen-Poiseuille equation

$$Q = \frac{\Delta P (dc)^4 \pi}{128 L \eta}$$

where

L is a predetermined length of tubing;

ΔP is the pressure differential or drop measured along the predetermined length of tubing;

dc is the diameter of the tubing; and

η is the viscosity of the solvent.

Since the pressure differential ΔP and flow rate Q are directly related, the flow rate Q can be indirectly measured using the proposed FMS. Therefore, the FMS indirectly measures or calculates the flow rate of the solvent into the column by monitoring the pressure differential ΔP across the tubing using two pressure transducers. The flow control valves 120, 120' are adjusted by motors 120, 120' to control the pressure differential ΔP and hence the flow rate Q of the solvents A, B. A closed loop system, as described here, will enable the ultimate control of the flow rates desired.

The user inputs at a computer 160 a desired gradient composition, e.g. 60:40 A:B, for each column in the array. The computer generates an analog signal that is transmitted to electrical circuits 155, 155', which control the motors 152, 152' so that the desired gradient composition input by the user at the computer matches the flow rate of the solvent based on the pressure differential as measured by the pressure transducers. If the pressure differential ΔP for the particular solvent is too high, hence the flow rate Q is too large, the stepper motor will start closing the associated valve until the targeted pressure differential ΔP is achieved.

It is the intended scope of the present invention to employ any conventional flow meter and valve in the flow control metering valves.

The present inventive parallel processing chromatographic system is advantageous in that the user can independently specify gradients for each column. Thus, the user can define various gradients for one experiment and then on the following experiment reconfigure the system for sample throughout by making all the gradients the same. Alternatively, different stationary phases can be tested in each column during a single experiment, again speeding up the method development time. Parallel processing in accordance with the present invention is an effective method to decrease cycle times. Currently methods can take up to a month, this invention has the ability to reduce these times by a factor of 10.

It is also desirable to develop a sample detection cell 135 with a longer path length compared to conventional detections systems. A longer path length enables lower detection limits. Figure 3 is an isomeric view of the fiber optic sample detection cell 135 in Figure 1a, 1b, 1c, 1d. Sample detection cell 135 is supported in a mounting block 305, which is disposed between two tee connections 315. Fiber optics 310 deliver and collect the light from the sample detection cell 135. The s-shaped configuration of the sample detection cell provides a longer flow path length and requires less space than conventional detection cells.

Figure 4 diagrammatically depicts an exemplary detection system for the 8 column array in Figure 1a. Light from a light source 405, such as a mercury arc lamp, is passed through a monochromater filter 410 to allow wavelength and bandwidth selection. The filtered light

passes through a bundle of fiber optics to illuminate all of the sample detection cells 135. A common detector 420, such as a charge coupled device or photodiode array, collects the absorbance data from all 8 columns and produces 8 chromatograms.

The benefits of the system proposed here is that the gradients can be formed using two pressurized solvent reservoirs instead, as traditionally required for 8 separations, of using 16 pumps for high pressure mixing or 8 pumps for low pressure mixing. The design not only saves money by combining 8 instruments thereby saving cost and space, but also allows for faster method development time and sample throughput by generating 8 chromatograms at once. As mentioned earlier, this can be expected to reduce the sample throughput and methods development times by at least a factor of 10.

In summary, the proposed HT-HPC in accordance with the present invention increases sample throughput, accelerates method development, and minimizes organic waste. HP-HPC parallel processing in accordance with the present invention is also suitable for mobile phase optimization, pH optimization, column screening, sample throughput, and preparative chromatography.

Thus, while there have been shown, described, and pointed out fundamental novel features of the invention as applied to a preferred embodiment thereof, it will be understood that various omissions, substitutions, and changes in the form and details of the devices illustrated, and in their operation, may be made by those skilled in the art without departing from the spirit and scope of the invention. For example, it is expressly intended that all combinations of those elements and/or steps which perform substantially the same function, in substantially the same way, to achieve the same results

are within the scope of the invention. Substitutions of elements from one described embodiment to another are also fully intended and contemplated. It is also to be understood that the drawings are not necessarily drawn to scale, but that they are merely conceptual in nature. It is the intention, therefore, to be limited only as indicated by the scope of the claims appended hereto.

ClaimsWhat is claimed is:

1. A high throughput high performance chromatography system operating at a high mixing pressure, comprising:

at least one pressurized solvent reservoir maintaining an associated solvent at a substantially constant pressure the number of solvent reservoirs equals the number of solvents;

a plurality of flow control valves connected downstream of said reservoir; and

at least one column connected downstream of said reservoir, said valves controlling the flow rate of the solvent into the respective columns.

2. The system in accordance with claim 1, further comprising an s-shaped sample detection cell for measuring absorbance.

3. The system in accordance with claim 1, wherein said solvent reservoir comprises one of a pump and an accumulator piston.

4. The system in accordance with claim 1, wherein each flow control valve comprises a valve and a flow meter.

5. The system in accordance with claim 1, wherein each flow control valve comprises a high-pressure solenoid controlled using pulse width modulation and a flow meter for metering a desired flow range.

6. The system in accordance with claim 1, wherein the number of flow control valves associated with each column is equal to the number of solvents.

7. The system in accordance with claim 1, wherein each flow control valve maintains a substantially constant flow rate of solvent.

8. The system in accordance with claim 1, further comprising a mixing device associated with each column for mixing the solvent output from at least two of said flow control valves.

9. The system in accordance with claim 1, wherein the system is one of a liquid, gas, fluid, microbore, capillary, preparative, and electro chromatography system.

10. The system in accordance with claim 1, wherein a gradient for each column may be independently specified.

11. The system in accordance with claim 1, wherein a plurality of columns are connected downstream of each flow control valve, said flow control valves controlling the flow rate of the solvent into the respective columns.

12. The system in accordance with claim 1, wherein a plurality of columns are connected upstream of each flow control valve, said flow control valves controlling the flow rate of the solvent from the respective columns.

13. The system in accordance with claim 1, wherein a plurality of columns are connected one of upstream and downstream of each flow control valve, said flow control valves controlling the flow rate of the solvents from the respective columns.

14. The system in accordance with claim 1, wherein the number of flow control valves associated with each lane is equal to a maximum number of different solvents to be mixed to form a gradient in the associated column.

15. The system in accordance with claim 1, further comprising a solvent selection valve disposed in each lane between the pressurized solvent reservoir and the flow control valve.

16. A detection system comprising:
an s-shaped sample detection cell for measuring absorbance.

17. The detection system in accordance with claim 16, further comprising a mounting block for supporting the detection cell.

18. The detection system in accordance with claim 17, further comprising fiber optics disposed on opposite sides of the mounting block.

19. A method for using a high throughput high performance chromatography system, comprising the steps of:

maintaining at least one solvent at a substantially constant pressure; and

controlling the flow rate of the solvent into respective columns using a flow control valve.

20. The method in accordance with claim 19, further comprising receiving a specified gradient for each column.

21. The method in accordance with claim 20, further comprising the step of independently adjusting the gradient for each column.

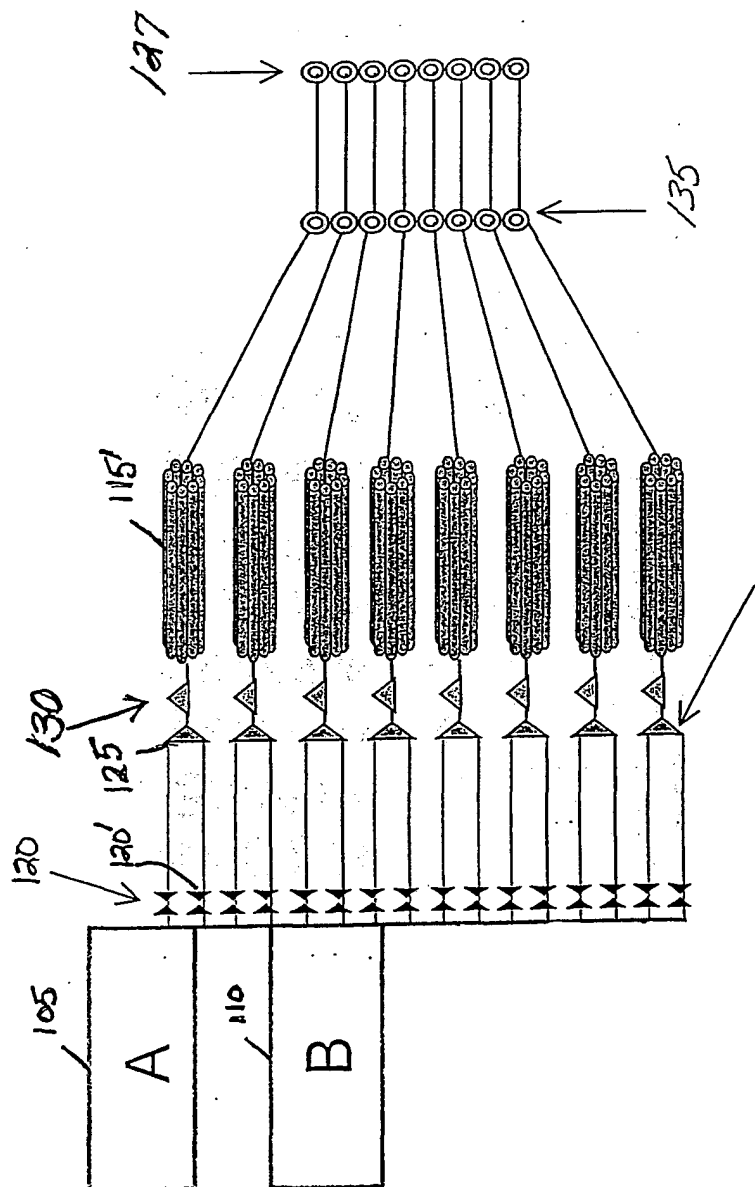


FIG. 1C

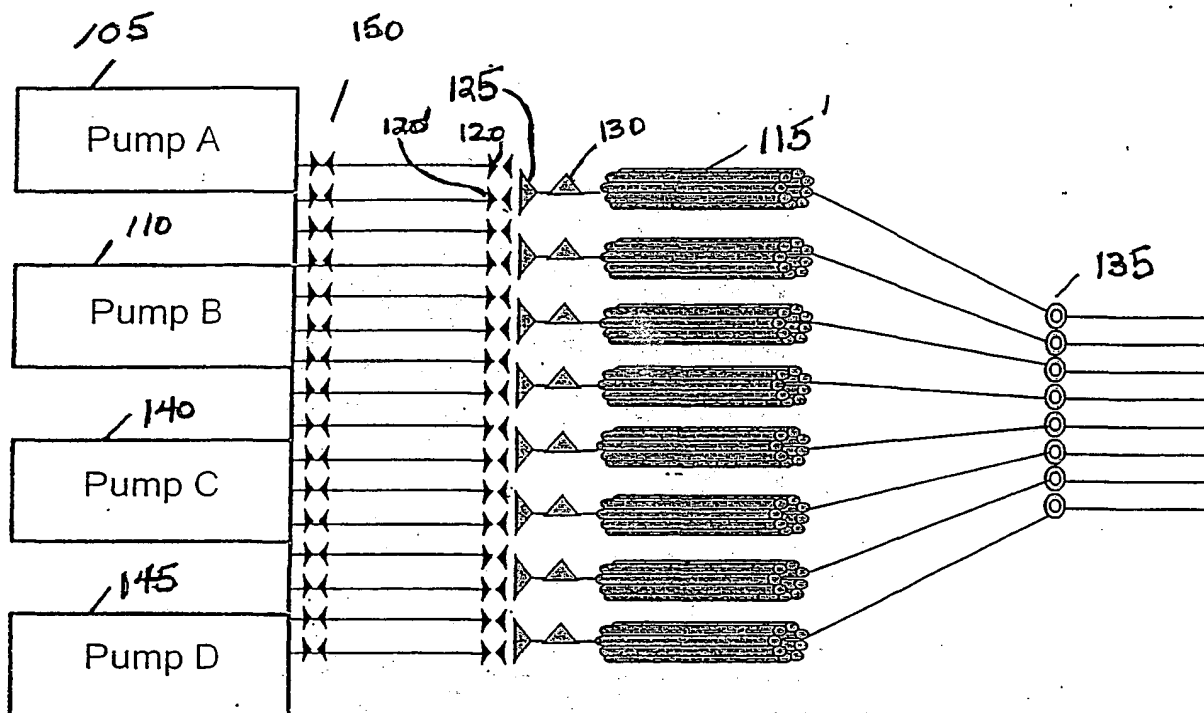


FIG. 1b.

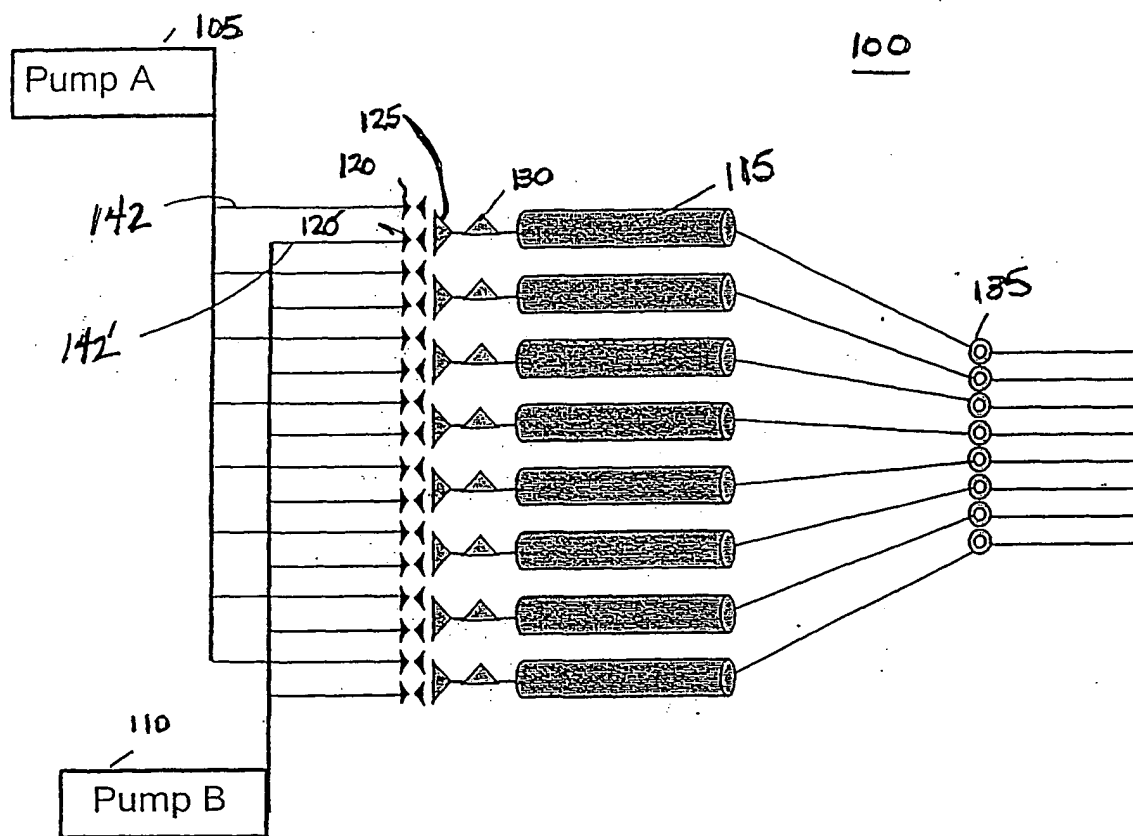


FIG. 1a

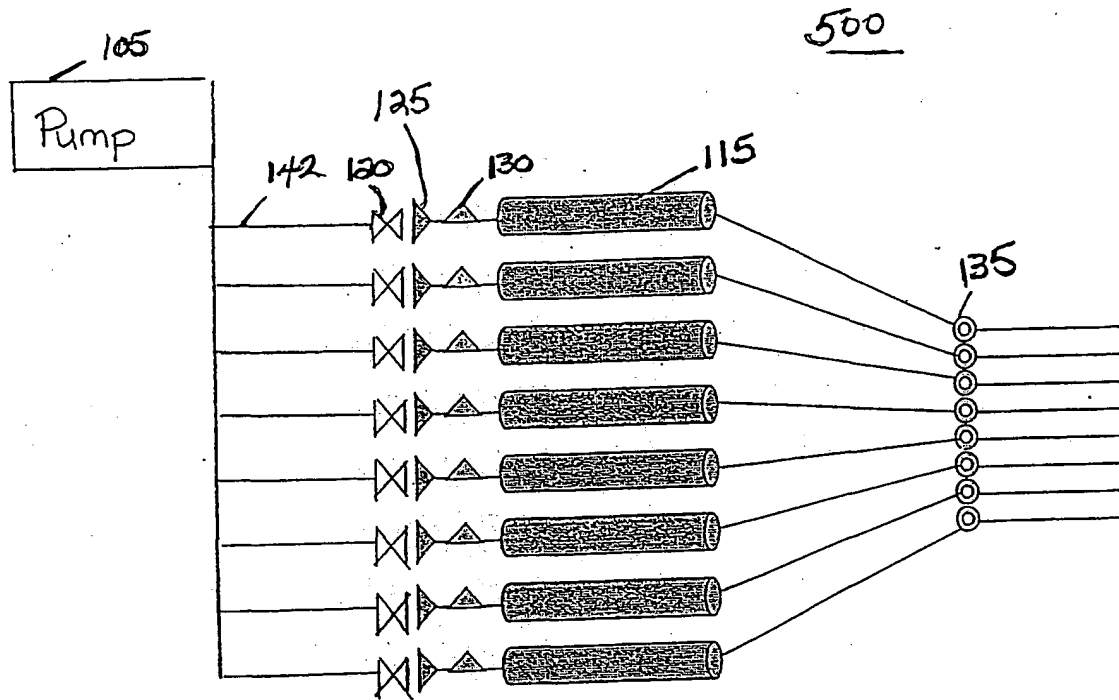
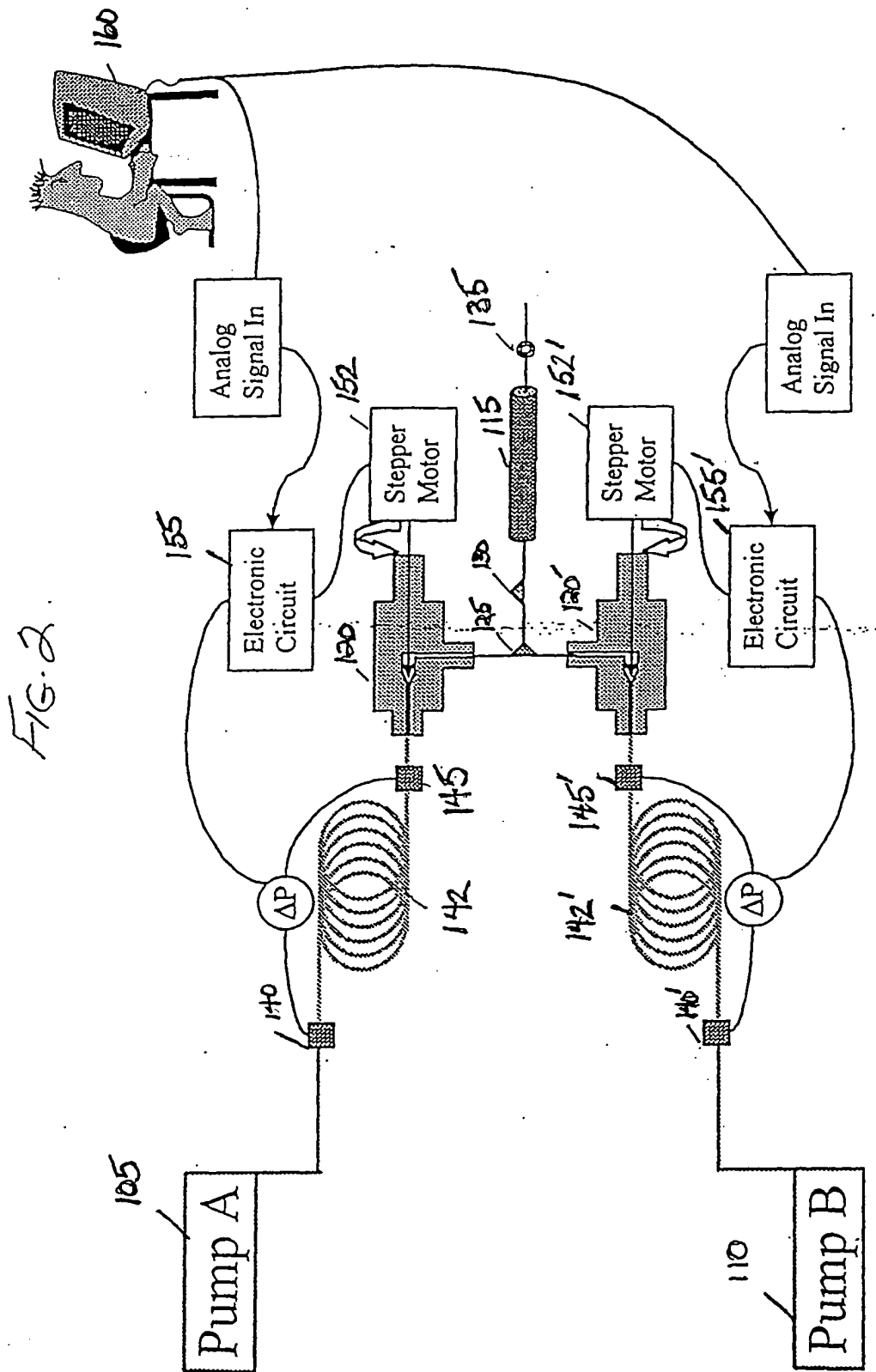


FIG. 1d



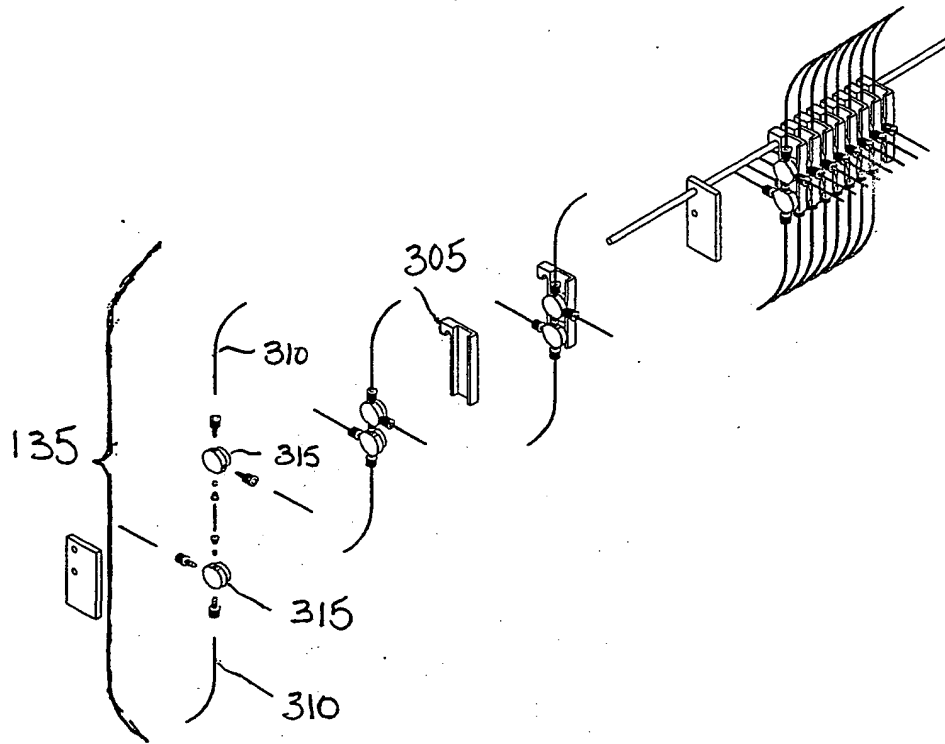


FIG. 3

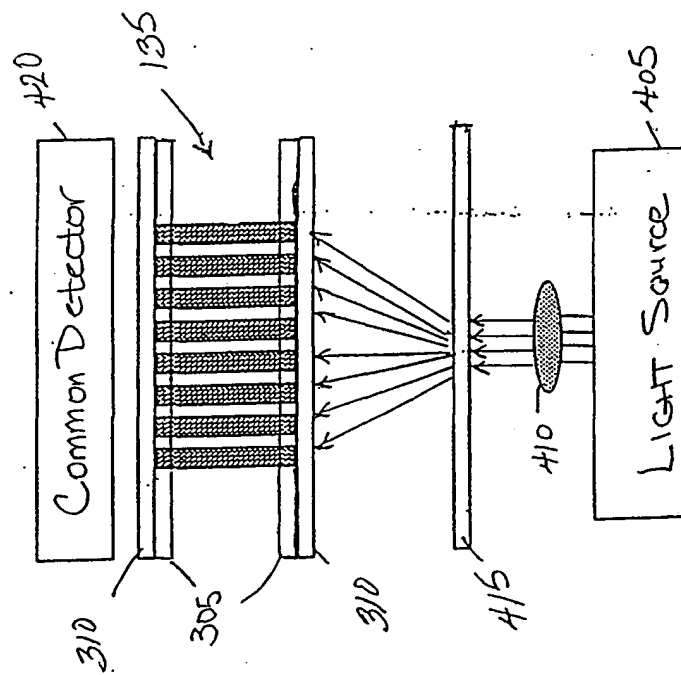


FIG. 4

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
18 July 2002 (18.07.2002)

PCT

(10) International Publication Number
WO 2002/056006 A3

(51) International Patent Classification⁷: **G01N 30/34**

(74) Agents: **JOHNSON, Philip, S.** et al.; Johnson & Johnson,
One Johnson & Johnson Plaza, New Brunswick, NJ 08933-
7003 (US).

(21) International Application Number:
PCT/US2001/051024

(22) International Filing Date: 23 October 2001 (23.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/699,212 27 October 2000 (27.10.2000) US

(71) Applicant: **ORTHO-MCNEIL PHARMACEUTICAL,
INC.** [US/US]; U.S. Route 202, Raritan, NJ 08869-0602
(US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA,
ZW.

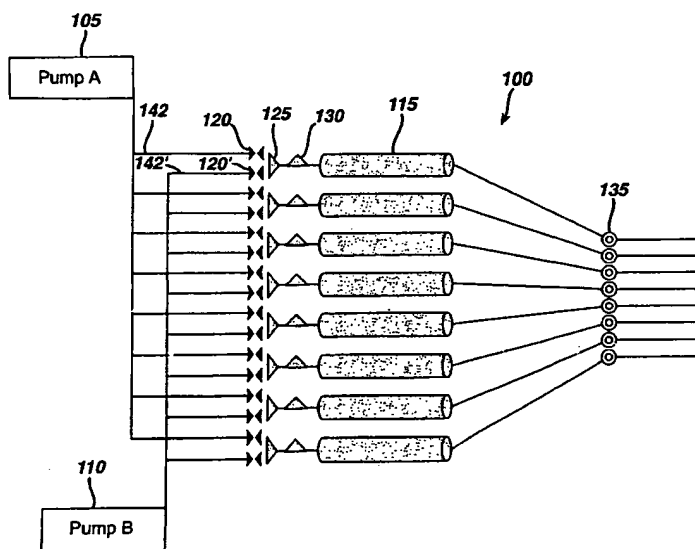
(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
TG).

(72) Inventors: **FERMIER, Adam, M.**; 76 Highlands Boule-
vard, Easton, PA 18042 (US). **HOCHMAN, Elias, H.**;
5-3 Aspen Way, Doylestown, PA 18901 (US). **GUZMAN,
Norberto, A.**; 17 Dellanbaugh Lane, East Brunswick,
NJ 08819 (US). **SCYPINSKI, Stephen**; 50 Kinnan Way,
Basking Ridge, NJ 07920 (US).

Published:
— with international search report

[Continued on next page]

(54) Title: HIGH THROUGHPUT HIGH PERFORMANCE CHROMATOGRAPHY SYSTEM



(57) Abstract: A high throughput high performance chromatography system operating at a high mixing pressure including a plurality of pressurized solvent reservoirs, e.g. pumps, each maintaining an associated solvent at a substantially constant pressure. A plurality of flow control valves are connected downstream or upstream of the reservoirs for controlling the flow rate of the solvent into the respective columns. The number of reservoirs equals the number of solvents. Accordingly, the system reduces the number of pumps required thereby saving money and space. Furthermore, the system increases sample throughput, accelerates method development and minimizes organic waste.

WO 2002/056006 A3



(88) Date of publication of the international search report:
19 February 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/51024

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 G01N30/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 800 784 A (HORN MARCUS J) 1 September 1998 (1998-09-01) column 16, line 26 - line 61 abstract	1-15, 19-21
X	--- US 4 669 502 A (LONARDI SILVANO ET AL) 2 June 1987 (1987-06-02) abstract -----	1

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

17 October 2002

Date of mailing of the international search report

20. 01. 03

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Moa Emling Grönkvist

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/51024

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-15, 19-21

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-15 and 19-21

Claims relate to a method for using chromatography maintaining at least one solvent at a constant pressure and controlling the flow rate.

2. Claims: 16-18

Claims relate to a detection system comprising an s-shaped detection cell

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/51024

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5800784	A	01-09-1998	AU 730411 B2	08-03-2001
			AU 3653297 A	10-02-1998
			CA 2259648 A1	29-01-1998
			EP 1015881 A2	05-07-2000
			JP 2000514563 T	31-10-2000
			WO 9803264 A2	29-01-1998
			US 6039924 A	21-03-2000
			US 6082417 A	04-07-2000
			US 6173603 B1	16-01-2001
			US 6168760 B1	02-01-2001
			US 6153437 A	28-11-2000
			US 6427731 B1	06-08-2002
			US 5918273 A	29-06-1999
US 4669502	A	02-06-1987	IT 1177277 B	26-08-1987
			EP 0182755 A2	28-05-1986
			ES 8700880 A1	01-02-1987
			JP 61122564 A	10-06-1986
			PT 81519 A ,B	01-12-1985

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)